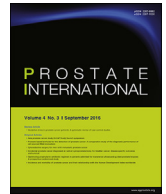




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Original Article

Asia prostate cancer study (A-CaP Study) launch symposium



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ABSTRACT

The Asian Prostate Cancer (A-CaP) Study is an Asia-wide initiative that has been developed over the course of 2 years. The A-CaP Study is scheduled to begin in 2016, when each participating country or region will begin registration of newly diagnosed prostate cancer patients and conduct prognosis investigations. From the data gathered, common research themes will be identified, such as comparisons among Asian countries of background factors in newly diagnosed prostate cancer patients. This is the first Asia-wide study of prostate cancer and has developed from single country research efforts in this field, including in Japan and Korea. The inaugural Board Meeting of A-CaP was held on December 11, 2015

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at the Research Center for Advanced Science and Technology, The University of Tokyo, attended by representatives of all participating countries and regions, who signed a memorandum of understanding concerning registration for A-CaP. Following the Board Meeting an A-CaP Launch Symposium was held. The symposium was attended by representatives of countries and regions participating in A-CaP, who gave presentations. Presentations and a keynote address were also delivered by representatives of the University of California San Francisco, USA, and the Peter MacCallum Cancer Centre, Australia, who provided insight and experience on similar databases compiled in their respective countries.

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1. Introduction

The Asian Prostate Cancer (A-CaP) Launch Symposium took place from 13:00 to 18:00 on December 11, 2015, at the Research Center for Advanced Science and Technology, The University of Tokyo and was attended by all members who had attended the prior Board Meeting, from 10 countries and regions in Asia (China, Hong Kong, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Taiwan, Thailand) and representatives of the University of California San Francisco (USA) and the Peter MacCallum Cancer Centre (Australia). The aim of the symposium was to mark the launch of the A-CaP Study by providing an overview of the present status of prostate cancer databases in Asia and discussing how each country or region would proceed with the A-CaP Study. Participants from the USA and Australia provided information on similar databases in their respective countries [Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) and the Victorian Prostate Cancer Registry (V-PCR)]. The following is a summary of the proceedings of the symposium.

2. Opening remarks

Hideyuki Akaza (Department of Strategic Investigation on Comprehensive Cancer Network, The University of Tokyo) expressed his pleasure to be able to welcome participants from 10 Asian countries, as well as from Australia and the USA. He noted a brief history of the collaboration of Japan (J-CaP), Korea (K-CaP), China (C-CaP), and CaPSURE.¹

Yoshihiko Hirao (Osaka Gyoumeikan Hospital) expressed his pleasure to be able to hold this launch symposium at the University of Tokyo. He explained that from 2 years earlier, efforts had been advanced towards the initiations of an Asian-wide collaborative study. One of the key issues was acquiring financial support and Yoshihiko Hirao expressed his appreciation to Hideyuki Akaza for working to amass funding. He expressed the hope that the meeting would be fruitful and would mark a good start for A-CaP.

Choung-Soo Kim (Urology Cancer Center, Asan Medical Center) thanked Hideyuki Akaza for his preparations for the launch of A-CaP, noting that he has been a key figure in working to highlight the differences in cancer between Asia and western countries. One of the key activities of A-CaP will be to create an Asia-wide database and encourage more and more institutions across Asia to contribute to a database. Another key issue for the future will be to give consideration to how best use the Asian database. Although there are still many challenges ahead, A-CaP is a most promising project and the Korean side is ready to contribute fully to the advancement of the A-CaP study and development of a database.

3. Seminar I: Present status of prostate cancer database study

Mototsugu Oya (Department of Urology, Keio University School of Medicine), Dingwei Ye (Department of Urology, Fudan University Shanghai Cancer Center), and Seichiro Ozono (Department of

Urology, Hamamatsu University School of Medicine) chaired Seminar 1.

3.1. Keynote speech: New findings from CaPSURE and introduction to AQUA

Matthew Cooperberg (Departments of Urology and Epidemiology & Biostatistics, School of Medicine, University of California San Francisco) noted that the collaboration between CaPSURE and J-CaP has been most rewarding and A-CaP promises to be a paradigm-changing study.

In the USA, as in other western countries, there is an ongoing drop in cancer mortality. The prostate cancer mortality rate has fallen by half since the 1990s. However, across the world, cases are still increasing, with 307,500 men dying from prostate cancer each year, the fifth most common cancer.

In terms of practice patterns in the CaPSURE register, data are abstracted from CaPSURE, a national registry of men with prostate cancer treated at up to 40 clinical practice sites, largely community-based, across the USA. CaPSURE has included people with localized disease since 1990, who have received treatment with radical prostatectomy (RP), external-beam radiation therapy (EBRT), brachytherapy, cryotherapy, watchful waiting (WW), active surveillance (AS), or primary androgen deprivation therapy (ADT). Risk stratification is implemented via a well-validated Cancer of the Prostate Risk Assessment (CAPRA) score. In terms of risk distribution over time, some of the first papers documented risk migration. Since the pre-prostate specific antigen (PSA) era, the risk has plummeted and since the 2000s risk migration has stopped and maintained at a steady rate. Surveillance is increasing in the real world and from the dawn of the PSA era the rate of AS/WW has increased significantly. The other trend is in the category of treatment of men with high-risk disease. A majority of men now receive RP.

In terms of trends for men older than 75 years there is still a tendency towards under-treatment. In terms of variation in individual practices there has been variation since 2010 across practices. There is a new registry called MUSIC, which is a statewide registry in Michigan. The insurance company in Michigan has provided millions of dollars into this registry and they pay for a data collector in every institution. Across the whole state, 49% of patients receive active surveillance. This represents a paradigm change about how low risk disease is treated in the USA.

In terms of comparative studies, the results of ProtecT are awaited and the results of other nonrandomized studies have been issued recently. Very few studies have looked at brachytherapy. Unadjusted cancer-specific mortality outcomes show that it takes a very long period to identify outcomes. It takes 15–20 years to identify differences between treatment modalities. The 15-year cancer specific mortality rates by CAPRA score for various treatments show that people with low risk disease do not have many differences. However, people with high risk disease show a significant difference in predicted 15-year cancer-specific mortality

depending on the kind of therapy received, whether it was RP, primary ADT, AS/WW, EBRT, or brachytherapy. In US populations, there is no role for ADT monotherapy for low-risk patients with localized disease. There may be a completely different scenario in Japan and Asia, however.

In the CaPSURE study, a little over 1% of people with low-risk cancer died of prostate cancer. As of 2015 there are just over 15,000 men in the registry and 179 publications have been issued. Up to 5,000 men are still followed actively. Continued follow-up for clinical and quality of life endpoints and collection of archived biospecimens for genomic analysis is being conducted. This part of the study has been enabled by grant funding and is likely to be a major focus for further research. CaPSURE will be collecting data from more and more domains in the future.

American Urological Association (AUA) Quality Registry (AQUA) is a new registry run by the AUA and the rationale is that prostate cancer requires clinical data, ideally collected prospectively. Existing clinical registry efforts have excellent track records in research and quality improvement, but are based on manual data collection and are difficult to scale. The key principles of AQUA are to use software (provided by FIGMD) to minimize data entry burden. Data ownership is by individual practices and the AUA only. Practice-level data will be shared only with individual practice, benchmarked against the aggregate data. No practice will see any other individual data. Patient-reported outcomes (PROs) will also be incorporated.

If the data are in the system as a structured data element, data extraction is simple. However, the Gleason score does not exist in a structured data format at present. However, there are natural language processing algorithms that enable the extraction of data from physician's notes, etc. AQUA was launched last year and there are now 660 urologists across 80 practices participating in the study. There is good geographic and practice-type diversity. For each quality measure, the practices can see where they are relative to an established benchmark and other participating practices on a dashboard.

There are three large community-based urology groups that will be administering PROs nationally. A patient dashboard will need to be added to the website that is being developed to enable PROs. From the first 16 practices in AQUA it has been possible to identify 194,415 unique patients, with 4,911 prostate cancer patients between 2014 and 2015.

CaPSURE has paved the way for US registry efforts in urology and other disciplines. The future must be collection of data from all men with prostate cancer, routinely at the point of care using automated systems. Data collection should include patient-reported outcomes. Integrating genomics will drive personalized medicine and answer questions, such as why prostate cancer varies internationally. PROs are no longer a research tool in the USA but a means of establishing the levels of quality of treatment. The A-CaP is an extraordinary effort and CaPSURE is honored to be a part of it.

3.1.1. Discussion

Shiro Hinotsu (Center for Innovative Clinical Medicine, Okayama University Hospital) noted that the presentation had included various data and asked about future prospective studies to collect parameters on comorbidity. Matthew Cooperberg responded that the competing risks analysis reflects comorbidities. It may be the case that men with comorbidities will suffer more side effects from treatment. The question of whether ADT causes cardiac disease is tremendously controversial, although nonrandomized studies have indicated that it does not. Questions about comorbidities are complex and there will be always confounding factors that cannot be accounted for.

Byung Ha Chung (Department of Urology, Gangnam Severance Hospital, Yonsei University College of Medicine) referred to the automated data retrieval system by an Indian company. Matthew Cooperberg responded that AUA has provided an initial budget for the first 5 years. Urology is the third national specialty in the USA, following cardiology and ophthalmology. In the long term it is considered that there will be enough value created that urologists will provide a participation fee. The hope is that there is going to be so much value that government and pharmaceutical companies will pay to conduct analysis using the registry. So far, no efforts have been made to recruit participants actively and the groups that have joined so far are just those that have expressed an interest. It will take many years before all urologists in the USA join the registry. It was noted that public reporting of data is now becoming a reality and if it is not controlled it will be done *to us* rather than *by us*.

3.2. J-CaP (Japan)

Shiro Hinotsu reported that the J-CaP 2001 study aimed to evaluate the trends and outcomes of hormone therapy for establishing an adequate guideline for hormone therapy in Japan. Data were collected using a secure server, with each institution inputting the data themselves. Over the course of 5 years a total of 26,272 patients were enrolled in the secure server. In terms of eligibility the patients were those who had been diagnosed by biopsy and who had started primary hormone therapy. In total, 19,409 cases were analyzed.

Initial hormone therapy was classified into various categories: antiandrogen (AA) monotherapy; surgical castration (SC) luteinizing hormone-releasing hormone agonist (LHRH) monotherapy; LHRH plus short-term AA; SC plus AA (SC+AA), LHRH plus AA; WW; and others. Approximately 60% of patients who started initial hormone therapy between 2001 and 2003 in Japan received LHRH+AA or SC+AA. Progression free survival was updated on September 30, 2014 and the median survival time is 4.94 years. Overall survival is 12.2 years.

There was a subgroup of patients who died from a cardiovascular event and these figures have been used to demonstrate that hormonal therapy did not increase cardiovascular events in patients.

In terms of cancer-specific survival in each cohort by J-CAPRA score, patients in J-CaP had a better cancer-specific survival than in the CaPSURE study.

A further study was the IS-1 study, which concentrated on patients with localized cancer (T1c or T2N0M0) who selected either hormone therapy or prostatectomy. A further study was J-CaP Surveillance 2010, which was conducted 5 years ago with the objective of seeing the time trend of patient characteristics at the diagnosis of prostate cancer and the time trend of initial treatment, using the datasets of the Japanese Urological Association from 2000 and 2004 for comparison.

In terms of the characteristics of J-CaP database, it can be summarized that the database contains long-term follow-up data (up to a maximum of 13.5 years) from a large number of registered patients. Data are provided by many hospitals in Japan. However, limitations of the J-CaP database are a lack of data on details of treatment change, PSA value during treatment and incomplete data on Gleason scores. With regard to further follow-up and new studies, a follow-up data collection of the IS-1 study and detailed analysis of J-CaP 2010 surveillance was implemented and a database of real world outcomes in Japan has been created. New observational studies will use a data structure consistent with J-CaP 2001, IS-1 and J-CaP 2010. The ethical committee of Okayama University has approved the new study protocol.

3.2.1. Discussion

Dingwei Ye asked what the most difficult part of maintaining a database had been for such a long time, noting that C-CaP had only recently started its own efforts and would like pointers concerning the way forward. Shiro Hinotsu responded that 15 years ago the computer system and network environment was completely different. Survivor data were essential and, although there were limitations in 2000, the data collection environment has been transformed and it is important to continue to maintain efforts to ensure data quality.

3.3. K-CaP (Korea)

Ji Youl Lee (Department of Urology, St. Mary's Hospital, The Catholic University of Korea) noted that there are the *Big Five* hospitals in Seoul—Seoul National University, Asan Medical Hospital, Samsung Seoul Hospital, Seoul St Mary's Hospital, and Yonsei Medical Center, from which cumulative data have been collected and delivered to the Korea Prostate Bank. Using the Korea Prostate Bank database, many papers have been published, including most recently a paper in *European Urology* in 2015 titled Prostate cancer registries: current status and future directions.²

A smart prostate cancer database is needed in Korea. This is needed because it is essential to have a common database structure. It is necessary to analyze the treatment outcomes of prostate cancer, including active surveillance, focal therapy, etc. It is also important to engage in analysis between clinical and basic research data, including biobank data, clinical data, and genomic profiles. Excel files will not be sufficient for big data analysis and open source software will be required, using cloud servers for ease of access.

The Multicenter Prostate Cancer Registry system in Korea uses three methods of data collection for prostate cancer: Excel on paper; a web based electronic case report form system; and clinical data warehouse system. Another important factor for data management is visualization tools. The Prostate Cancer Research Network has amassed a total of 8,510 patients to date. The database is mainly based on RP, in contrast to the J-CaP database. A prostate cancer committee has been established among the major hospitals and this committee makes decisions on who may use the joint database to engage in analysis.

There is an international consortium plan in Korea, under which if countries or institutions seek to use the Korean database system they may do so for a small maintenance fee, with the system using an open source database structure for facilitating international collaboration based on cloud servers. This Smart Prostate Cancer Database system is available in three languages and has been used on a pilot basis by Hong Kong and Indonesia. Clinical and basic cancer research in the near future will incorporate medical informatics (big data) with bio banking and genomic profiling (nano data), which, it is anticipated, will result in the realization of personalized medicine. Korea is also in the process of developing an electronic genomic medical record system.

In terms of the future for the A-CaP study, it would be preferable to move towards a clinical decision-supporting system, including a clinical database—biobanking—genomic database integration system, which could help lead development towards the realization of personalized medicine.

3.3.1. Discussion

Shigeo Horie (Department of Urology, Juntendo University Graduate School of Medicine) noted that the presentation had been very wide-ranging. He asked about confounding factors and how these could be incorporated into databases when considering the modalities for treatment. Ji Youl Lee responded that

data from a diabetic study had been accessed through data mining. Big data always can provide the answer. The question is how to find the data that are needed and use them towards the objectives of the K-CaP database. Clinical data alone are not as useful anymore.

3.4. C-CaP (China)

Gang Zhu (Department of Urology, Beijing United Family Hospital and Clinics) noted that there was an urgent need for a database similar to J-CaP, K-CaP, and CaPSURE in China. According to the National Central Cancer Registry of China 2015 annual report, the overall incidence of prostate cancer was 7.1/10⁵ population in 2011. This figure ranked ninth in the highest cancer incidences for all sexes and seventh in men.³ In response to this need, Na Yanqun proposed to establish the Chinese Prostate Cancer Database after discussion with Hideyuki Akaza. The C-CaP software design was initiated in September 2013. The aim of C-CaP is to collect and manage Chinese prostate cancer patient data in diagnosis, treatment, and follow-up, to provide good evidence for better diagnosis and treatment of prostate cancer, to provide education materials to patients and to establish a platform for international exchange. In C-CaP diagnosed prostate cancer, patient data are being prospectively collected. Each C-CaP center can access C-CaP software to manage and study its own patients for free. The C-CaP committee issues Chinese data and participates in international studies.

The starting point of C-CaP software is to serve C-CaP centers to better manage and use their own prostate cancer patient data. C-CaP software has been designed to be simple and convenient and be easy to operate. The English version has recently been completed and will be used in Hong Kong, Macao, and other locations. C-CaP was officially announced and released to the public in December 2014. Currently there are 73 C-CaP centers in China with 4,602 patients recruited. The main functions of C-CaP can be summarized as being to set up a database, engage in follow-up, check data, engage in analysis, and export data. C-CaP apps have also been developed for both doctors and patients.

Challenges that still need attention include such issues as how to effectively increase records submitted to the database. Another key issue relates to legal issues and addressing the questions of whether consent needs to be sought from every patient and how to protect patient privacy. Testing of the developed apps is ongoing with a view to deploying these apps fully in the future.

3.4.1. Discussion

Bannakij Lojanapiwat (Faculty of Medicine, Chiang Mai University) asked about system differences between K-CaP and C-CaP. Gang Zhu responded that coding items are based on those of J-CaP, making it easy to manipulate data and make data interoperable. It is also possible to abstract data directly and selectively to facilitate operations. It is also possible to extract data in Excel format.

Wun-Jae Kim (Department of Urology, Chungbuk National Medical University Hospital) asked whether it was possible to transmit personal information. Gang Zhu responded that personal information is kept exclusively in the hospital where the patient was registered and cannot be seen by anyone else.

Edmund Chiong (Department of Urology, University Surgical Cluster, National University Health System, Singapore) asked about legal consent and how C-CaP proposes to gain consent. Gang Zhu responded that a consent form is being compiled and will be provided to patients. However, there should not be any concerns as no patient data will be sold.

4. Seminar II: How to proceed with the A-CaP Study

How to establish with the A-CaP Study: perspectives in participating countries

5. Part I

Mikio Namiki (Graduate School of Medicine, Kanazawa University), Shigeo Horie and Byung Ha Chung chaired part I of seminar II.

5.1. Taiwan

Chung-Hsin Chen (Department of Urology, National Taiwan University Hospital) talked about the best way to proceed A-CaP in Taiwan. He noted that the best way would be to link to the established database in Taiwan, of which there are two, the Taiwan Prostate Cancer Consortium (TPCC) and Taiwan Cancer Registry Database (TCRD). There are possible expected obstacles, which are the low input rate for TPCC and limited parameters for TCRD.

There are approximately 5,000 newly diagnosed cases of prostate cancer in Taiwan each year. In 2011 prostate cancer was the fifth leading cancer in men. The proportion of prostate cancer has increased dramatically, from 1.85% in the early 1980s to 8.91% in 2011.

From 1979 the government started to create a cancer registry. The TPCC has its origins in the objective to make up the limitations of the TCRD and include important clinical parameters. The TPCC was established in 2012, with a total of 18 hospitals currently participating, with 16,385 patients enrolled. The TPCC covers almost all regions in Taiwan.

The Urological Oncology Committee receives data reports from hospitals and provides TPCC whole cohort feedback to hospitals. Database collection forms include personal basic data, risk factors, initial clinical presentation, initial tumor status, initial treatment, AE and response, and oncological and survival outcomes. There are a total of 139 items. There is debate in Taiwan on how to define data. A consensus meeting was held in November 2013 and it was determined that data should be based on DRE and record additional stages.

The most common initial PSA is < 10 ng/mL, but 18% of patients have a PSA of > 100 ng/mL. The most common cancer staging in Taiwan is T2 (36%). In terms of cancer-specific survival there is no specific difference between Stage 1 and 3 cancers, which is 98% for 5-year survival and 96% for 10-year survival. In terms of overall survival, there is a greater difference between Stages 1 and 3, although this could be due to the advanced age of patients with highest cancer staging.

5.1.1. Discussion

Matthew Cooperberg asked about increased incidence and asked if this is due to the aging of the population. Chung-Hsin Chen responded that there is no prostate cancer screening system in Taiwan, but more and more people are taking their own health check-ups. Tong-lin Wu (International Medical Center, Kaohsiung Veterans General Hospital) responded that although there is no national screening urologists are required to provide a PSA test to males that they see who are older than 50 years.

Mikio Namiki asked about the percentage of hospitals participating in the TPCC. Chung-Hsin Chen responded that 23 hospitals initially indicated that they would participate, but to date only 18 have been inputting data.

5.2. Hong Kong

Ng Chi Fai (Division of Urology, Department of Surgery, The Chinese University of Hong Kong) reported that prostate cancer is now the third most prevalent cancer among men in Hong Kong. A

government-funded body is responsible for the management of public health services in Hong Kong, which covers > 80% of care. There is a clinical management system in Hong Kong that utilizes electronic consultation notes and covers the entire territory. The integrated records of patients are comprehensive and easy to access.

In terms of the HK-CaP database, preparation work has already been implemented, with a view to participating in A-CaP. A protocol has been formulated with centers being invited and an online database being constructed. The hospitals that are expected to participate are located in all areas of the territory. The online database input form includes a variety of items and it is still under development. After seeing the K-CaP and C-CaP databases, these will provide an excellent source of reference for future development of the HK-CaP database.

5.2.1. Discussion

Hideyuki Akaza asked how Hong Kong would manage discrepancies or differences between the A-CaP database and the proposed HK-CaP database. Ng Chi Fai responded that the database is still under construction and there is still time and scope to expand the items that would be included. The database already includes the basic items that would be required by A-CaP.

5.3. Indonesia

Lukman Hakim (Department of Urology, Airlangga University/ Dr. Soetomo General Hospital, Surabaya) reported that prostate cancer is the sixth most prevalent cancer in the world. In terms of the recent status of prostate cancer in Asia, he cited a report *Prostate cancer in Asia: a collaborative report*,⁴ which was published in the *Asian Journal of Urology* and included the results of a multicenter longitudinal study in Indonesia. In terms of the mortality to incidence ratio, this ratio is high in Indonesia in comparison with other Asian countries. In terms of the epidemiology of prostate cancer in Indonesia, a multicenter study of five tertiary hospitals showed that the median age of diagnosis is 68 years and most patients are in their 60s and 70s at diagnosis. The median PSA at diagnosis is 60.2 ng/mL. In comparison to the above-mentioned report, a PSA level of over 20 ng/mL is significantly greater in Indonesia than in other countries covered in the report.

In terms of diagnostic methods, 81.4% of cases are conducted using a biopsy. In terms of T and M staging there is a large proportion of metastasis (M1c), which suggests that people in Indonesia are reluctant to go to hospital if they feel unwell.

With regard to treatment modalities, the most common treatment is orchiectomy (32.1%), followed by medical castration (25.3%) and radical prostatectomy (13.4%). The reason for the high rate of orchiectomy is that patients tend not to return to hospital after medical castration, so orchiectomy is utilized.

With regard to other studies, two tertiary care hospitals in Jakarta engaged in a study from 1995 to 2013 and this study showed that the median age of diagnosis was 68 years, with a median PSA of 50.78 ng/mL. This study was consistent with the report mentioned above. In terms of treatment modalities, 13.8% of patients refused treatment in the Jakarta study, which represents a problem for Indonesia. This is not due to monetary issues, as low income people in Indonesia are now fully covered by the health insurance system.

Survival analysis of 107 elderly patients who underwent treatment for localized or locally-advanced cases in two tertiary hospitals in Indonesia showed no significant differences in the 5-year survival rate.

In terms of treatment options for localized and locally advanced prostate cancer, although there are no significant differences among Asian countries in hormonal therapy, there is a low use of RP in Indonesia.

Prostate cancer in Indonesia has been increasing in the last decade. Locally advanced and metastatic disease are dominant. Primary ADT with or without radiotherapy is the most common treatment for localized and locally advanced cancer. Surgical castration is still commonly recommended for advanced cases, with RP being less applied than in other countries in Asia, Europe, and the USA.

With regard to how to proceed the A-CaP study in Indonesia, there are three cancer centers on Java Island—Bandung, Jakarta, and Surabaya—which each have several satellite hospitals. It will be a challenge to include other hospitals in order to get a larger national picture. For the A-CaP study the three cancer centers on Java Island will be participating, using their satellite hospitals. Regulations in Indonesia allow physicians to work in up to three medical institutions, which should provide more opportunities to gain samples for the A-CaP study. The data items to be collected will be in line with the proposal from J-CaP. It would be preferable for website-based data collection on good clinical practice principles. The first A-CaP meeting is scheduled to take place in Indonesia in February 2016.

5.3.1. Discussion

Shigeo Horie asked about ideas for implementing follow-up in Indonesia. Lukman Hakim responded that, given the size of the country, follow-up would be difficult. Follow-up could be achieved by offering incentives to patients to travel to hospitals (provision of travel expenses, etc.), or, if necessary, providing home visits.

Hideyuki Akaza asked about the main reason for patients refusing treatment. Lukman Hakim responded that in the past when the national health insurance system was not effectively implemented, there were cost issues that presented obstacles. In addition, there is a cultural resistance to having surgery. Recently the national insurance system has improved but the cost allocation for the family member who accompanies the patient to hospital remains with them during their hospitalization may need further attention.

5.4. Singapore

Edmund Chiong reported that prostate cancer is the third most common cancer in Singapore men. There are 28.5 cases per 100,000 men and it is the sixth leading cause of death. Prostate cancer incidence has steadily risen over the years and mortality rates have also steadily increased. There has also been some variation in incidence and mortality among the various ethnicities in Singapore.

There are seven public hospitals (one under construction) in Singapore, which are covered by four health systems. In terms of existing resources there is a national cancer registry, the Singapore Cancer Registry, but there is no comprehensive data collection on investigative or treatment data. Prostate cancer databases exist only in individual hospitals and academic institutions. Prostate cancer studies have been implemented in Singapore, including interventional trials, advanced prostate cancer observational studies, post-ADT observational studies and a Movember database. Three hospitals have indicated their readiness to participate in the A-CaP study. Other avenues for recruitment of patients include medical oncology and radiation oncology departments, other institutions in the country, and contact with academic societies, such as the Singapore Urological Association.

In terms of challenges, the funding of research assistants could be cited. Research assistants are currently grant funded rather than being permanent staff. There will also need to be accurate follow-up data and oversight. There is an opportunity that other observational and interventional studies may be competing with A-CaP, causing research assistant and investigator fatigue. In addition, time will be needed for contractual agreements between institutions and with A-CaP, on data sharing, which may delay the

timeline somewhat. There are strict data protection laws in Singapore and the acquisition of consent and institute review board (IRB) approval will also be an important issue.

5.4.1. Discussion

Shigeo Horie asked about metastatic disease in Singapore. Edmund Chiong responded that there is no national screening program, but there are an increasing number of health checkups available, which contributes to the increase in diagnosed prostate cancer incidence.

Hideyuki Akaza referred to the acquisition of consent and IRB and asked how long it could take for IRB applications. Edmund Chiong responded that IRB applications generally take 3 months. There are other options of building a standing database within an institution, but this would also require approval. Hideyuki Akaza noted that the multiethnicity of the Singapore population could make it an important source for data analysis. He asked about treatment outcome differences among ethnicities. Edmund Chiong noted that there is no evidence to suggest that some ethnicities respond better to treatment than others. He noted that the bulk of data is for Chinese ethnic people. The incidence of prostate cancer is slightly higher among ethnic Chinese than other ethnicities.

5.5. Philippines

Jason L. Letran (Department of Urology, Cardinal Santos Medical Center) reported that there is no detailed cancer database in the Philippines. The most recent data available show that among the number of new cases for the 10 most common cancers in 2010, prostate cancer is the fourth most common.

In terms of prostate cancer management in the Philippines over the last 25 years, before the 1990s there was no early detection strategy in place and most cancers were detected in advanced stages. From the 1990s to 2000s PSA came to be used more widely and cancer was detected in earlier stages. From the 2000s onwards there has been a rapid development in treatment, including brachytherapy, cryotherapy, and laparoscopy.

There is a National Digital Rectal Examination Day in the Philippines, which is held on the day before Fathers' Day each year. On this day free consultations are provided nationwide and this could be a good source of data for A-CaP. Each year, approximately 3,000 examinations are implemented. The Philippines Society of Urologic Oncologists, Inc. is a special interest society with 13 founding members and 104 members. The vision of the society is to lead organization in urological oncology in the Philippines. The society seeks to create a Philippines Prostate Cancer Database. The expected launch of this database is June 2016 and the objective is to have a longitudinal observational study of patients diagnosed to have prostate cancer in the Philippines.

The database will have the involvement of 11 training institutions and 20 private institutions. This would provide a good source of patients for A-CaP. Urologists would provide methods of screening, PSA values at diagnosis, diagnostic and pathological Gleason score and stage, among other items. Although institutions are not sufficiently advanced to cope with electronic data entry, it is hoped to provide a data sheet with online data entry and a dedicated data encoder. This is the template by which the Philippines would aim to participate in the A-CaP study.

5.5.1. Discussion

Byung Ha Chung asked about workload in the Philippines, given the very small number of urologists across the country. Jason L. Letran responded that the situation is difficult but the urologists work hard around the country. Hideyuki Akaza asked about refusal of treatment and asked if it would be possible to provide figures on this.

6. Part II

Rainy Umbas (Faculty of Medicine, University of Indonesia), Kazuhiro Suzuki (Department of Urology, Gunma University Graduate School of Medicine), and Kazuo Nishimura (Department of Urology, Osaka Medical Center for Cancer and Cardiovascular Diseases) chaired part II of seminar II.

6.1. Malaysia

Teng Aik Ong (Division of Urology, Faculty of Medicine, University of Malaya, Kuala Lumpur) reported that there are 108 urologists in Malaysia, serving a total population of 30 million. There is no up to date cancer registry in Malaysia, the most recent figures available being for 2007. Prostate cancer is the fourth most common cancer among men and is more prevalent in ethnic Chinese. A large proportion (almost 40%) of prostate cancer patients present with stage 4 metastatic cancer.

Urological services are provided by both the government and private sector, including Ministry of Health hospitals and university teaching hospitals, as well as private hospitals. After inquiring with institutions about the possibility of participating in A-CaP, the assistance of J-CaP, etc., will be required to facilitate approval from the government for state-run hospitals. If government hospitals can be covered, that would mean that the majority of regions and patients could be covered under the A-CaP study.

In terms of strategy, issues that need to be addressed include concerns over patient consent, ethics approval, funding, leadership, and moves to expand the scope of the study.

6.1.1. Discussion

Rainy Umbas asked about any envisaged challenges relating to data collection. He asked whether it would be important to formulate guidelines. Teng Aik Ong responded that the methods of diagnosis and treatment are more or less the same across the country and successful data collection will be reliant on the urologists themselves.

6.2. Thailand

Bannakij Lojanapiwat noted that although the incidence of prostate cancer in Asia is lower than western countries, the stage of prostate cancer at diagnosis in Asia is higher than western countries. Prostate cancer incidence has been rising steadily in Thailand over the last 2 decades, but is still very low compared to other Asian countries. The ratio between mortality and incidence is high in Southeast Asia in contrast to other countries in Asia.

Given the low incidence, PSA screening is not a routine practice in Thailand. The test is usually implemented in patients who complain of lower urinary tract symptoms or individual requests for screening. In a study entitled Correlation and diagnostic performance of the prostate-specific antigen level with the diagnosis, aggressiveness, and bone metastasis of prostate cancer in clinical practice (Prostate International)⁵ it was found that the patients' average age was 68 years and the average PSA level for biopsy was 102 ng/mL. A positive biopsy result was found in 396 patients. The study showed the prevalence of prostate cancer to be 35.39% and the positive predictive value in the diagnosis of prostate cancer when the PSA level was > 4 ng/mL to be 37.2%, which is a little higher than in a pooled meta-analysis study (25%).

Transrectal ultrasound with a prostate biopsy is the recognized procedure for a diagnosis of prostate cancer. Due to the high rate of fluoroquinolone-resistant bacteria in most hospitals in Thailand, patients who have risk factors to develop sepsis should have rectal swab cultures for antibiotic susceptibility testing before a

transrectal ultrasound with biopsy. Treatment of prostate cancer depends on clinical risk classifications such as D'Amico risk grouping or National Comprehensive Cancer Network risk grouping. In Thailand, urologists usually classify the patients following National Comprehensive Cancer Network guidelines (Asian Version). Local Prostate cancer guidelines by Thai Urologic Association were issued in January 2013.

The healthcare insurance system in Thailand provides full coverage through four systems, the major one of which is the Universal Coverage Scheme, covering 74.6% of the population. Life expectancy and comorbidity are important factors in the valuation and treatment of prostate cancer in Thailand. In real-life practice, most treatment of localized prostate cancer in Thailand is a RP including open RP, laparoscopic RP, and robot-assisted RP in any risk classification (low, intermediate, or high risk) of healthy patients younger than 70 years.

In terms of the A-CaP study it is anticipated that in collaboration with the Thai Urologic Association, data collection will be implemented in five large hospitals in Bangkok and one large hospital in Chiang Mai and Songkhla.

6.2.1. Discussion

Rainy Umbas noted that the situation in Thailand is similar to Malaysia and the Philippines. He asked about policies for follow-up for 5 years or 10 years. Bannakij Lojanapiwat responded that there should be no problem with follow up in university hospitals.

6.3. Taiwan

Tong-lin Wu reported that the existing databases in Taiwan were created for academic purposes, but not on the basis of any specific theme. The National Prostate Cancer Registry (NPCP) is run by the Government, which pays for people to input data. The NPCP is participated by 80 hospitals currently. Although the items to be registered are not very comprehensive, nonetheless they tend to be fully filled. In contrast, the TPCC is more comprehensive, but tends to be less fully filled out.

The NPCP requires that patient data should be registered 1 year after diagnosis, and the status must be updated every 3 years thereafter. The median age of diagnosis in Taiwan is 74 years with 55% of all cases being T1 or T2. Currently there are a total of 19,285 registered patients, with the number registered rising steadily each year. Among the treatments for prostate cancer EBRT accounts for the largest percentage (44%), followed by ADT (29%) and transurethral RP (22%).

In terms of the commitment of Taiwan to joining the A-CaP Study, six tertiary medical centers will join and all PIs are KOL, with experience in CaP-related trials. Taiwan will contribute 1,500–3,000 cases over the course of 3 years. The A-CaP study protocol will be strictly followed and Taiwan is willing to collaborate with any other colleague wishing to use the Taiwan database.

6.3.1. Discussion

Kazuhiro Suzuki asked about the percentage of patients enrolled in the national database. Tong-Lin Wu responded that approximately 95% of T1 and T2 patients are registered in the national database. In addition, 98% of patients are covered by the national health insurance.

6.4. Korea

Wun-Jae Kim noted that the reason that A-CaP is being implemented to seek an answer to the question of whether the characteristics of prostate cancer differ between races. The CaPSURE study has a large cohort with all stages of CaP and has issued 179 research

papers. In Asia, there are currently only national study groups, including J-CaP and K-CaP, but until now there has not been any unified study across Asia. CaPSURE is one of the leading prostate cancer registries in the USA, although urology practices are over-represented and radiology practices are underrepresented, with only diagnostic and therapeutic studies ordered by participating physicians being recorded. A-CaP is still in its incipient stages and many things remain still to do.

When organizing A-CaP it will be important to consider questions such as: How to collect data? What kind of committee should manage A-CaP? What kind of server should be used? How to decide the topic for publication? There are already existing databases in Asian countries, including J-CaP, K-CaP, and C-CaP databases. These are nationwide longitudinal prospective cohort studies, with detailed data on type of ADT. The K-CaP database is a comprehensive data base for CaP patients in Korea, including collection of tissue specimens and urodynamic data. C-CaP has also recently launched and other countries in southeast Asia are advancing moves to create databases.

Another important issue will be the management of the server for A-CaP. It will be important to use a common server for direct data collection, which could be a cloud server, linking to each country's server, although the final details have still to be worked out.

In terms of committees, the A-CaP will include various committees. The Steering Committee will be presided over by the President and comprise representatives from each country who will attend general meetings. This committee will have to decide what kinds of other committees will be required. The Committee for Policy-making will be moderated by the president of A-CaP and should be responsible for policy-making, management, and surveillance. The Data Committee will be a very important committee, responsible for collecting data from 10 Asian countries. Matters that need consideration are whether each country needs to be represented and what kind of data (items) are required, including pre-operative data, operation data, hormone therapy data, and castration-resistant prostate cancer-related data. Sometimes it may be necessary to change the items for A-CaP and the Data Committee should be responsible for such matters. The Scientific Committee will be responsible for determining research themes and such matters as who will be in charge of specific topics for publication.

6.4.1. Discussion

Hideyuki Akaza noted that more discussion will be required to make A-CaP more robust. He thanked Wun-Jae Kim for his presentation.

6.5. Australia

Declan Murphy (Division of Cancer Surgery, Peter MacCallum Cancer Centre) reported on perspectives from Australia and New Zealand. He noted that the paper Prostate cancer registries: current status and future directions² shows the benefits and advantages of registries. It was noted that it is pleasing to see that much of this work to create registries is up and running in the Asia-Pacific region.

Australia and New Zealand have very high incidence of prostate cancer. The indigenous populations fare poorly in terms of survival in both countries, which were reported in the BJU International last year, and this is why Australia is interested in participating in the broader Asian region.

There are two registries in Australia: the Victorian Prostate Cancer Registry (V-PCR), which was established in 2008 and now has 15,000 patients in the register; and the South Australia Prostate Cancer Clinical Outcomes, which was established in 1998 and has accumulated over 10,000 patients.

The goals of the V-PCR are to provide information on patterns of care following diagnosis of prostate cancer, to monitor quality of care and to provide a platform for further research of prostate cancer. The registry is very successful at recruitment, with 90% of all new prostate cancer diagnoses registered at 33 sites. There has been 100% clinician opt-in and 98% patient opt-in.

In terms of the management of localized prostate cancer, AS is the most used treatment for low risk cancer, and surgery is the most popular option for intermediate risk cancer, similarly to the USA, with robotic surgery being the most used. In terms of PROs, urinary functions and sexual functions are the most reported. Interestingly, radiotherapy patients report more trouble with urinary function than surgery patients.

One of the reasons that clinicians like to participate is that the registry sends regular reports to clinicians and hospitals, including information such as mortality rate, positive margins, documentation of T stage in medical record, treatment for men with high risk disease, no treatment for men with very low risk disease, treatment failure and biochemical recurrence at 24 months. These reports can be used by clinicians and hospitals, and are a good way to monitor the quality of care provided to patients. The register and feedback method has helped to achieve a 21% reduction in rate of low-risk cancer undergoing active treatment since 2010. Many publications have been issued based on V-PCR. It is an excellent disease-specific registry with almost population-level data capture. It provides a good platform to expand the registry nationally.

The South Australia Prostate Cancer Clinical Outcomes recruited 915 patients in 2014 and they have not issued many publications, but they are a partner in the new national database, known as the Prostate Cancer Outcomes Registry Australia and New Zealand (PCOR-ANZ). This registry is funded by Movember Foundation, which raised US\$100 million over the past year and PCOR is one of the key initiatives it is supporting. An award has been given to establish the new database PCOR-ANZ. Data collection and IT aspects are already up and running and it is hoped that all cases in Australia will be recorded on the new database. The PCOR-ANZ will provide a bi-national, population-based registry using International Consortium for Health Outcomes Measurement data.

Movember are supporting a global effort to coordinate prostate cancer outcome registries and it may be useful for A-CaP to align with the Movember Foundation and perhaps seek funding.

6.5.1. Discussion

Kazuo Nishimura noted that the focus on quality was very interesting. Declan Murphy responded that this is one of the government requirements as a means of improving quality of service provision.

Peter Carroll [Departments of Urology and Epidemiology & Biostatistics, School of Medicine, University of California San Francisco (UCSF)] commented on tracking positive margins as a quality indicator, noting that positive margins could have adverse outcomes by encouraging clinicians to operate more on low-risk patients. He pointed out that UCSF has experience of showing that positive margins do not have the impact of other items.

Hideyuki Akaza noted that A-CaP has much to learn from the experiences of Australia and the USA and that it will be a useful source of comparison. He requested the continued support and advice of Australia, noting that it is hoped an A-CaP symposium could be held on an annual basis.

7. Special lecture: AS for early-state prostate cancer—UCSF experience

Osamu Ogawa (Department of Urology, Graduate School of Medicine, Kyoto University) chaired the special lecture.

Peter Carroll noted that CaPSURE started in 1995 and it has been astonishing to see how the rest of the world has raced forward in the past 20 years. There is great enthusiasm and forward momentum occurring in Asia.

The goal of AS is to avoid or delay the costs of treatment without compromising cancer care. This is based on the rationale that initial assessment is reasonably accurate and monitoring is accurate and identifies subclinical progression at a time that initial treatment options are still available and curative.

The over detection of prostate cancer is a risk of PSA testing. One of the possible solutions is to reduce treatment of lower-risk tumors or change screening guidelines so as to decrease over-detection by not screening for low-risk disease.

A cohort at UCSF in 2015 has 1,400 patients enrolled with median follow-up of 53 months and median PSA of 5.3 ng/mL. There are 82% low risk patients and 18% intermediate risk patients. At UCSF, PSA testing is conducted at 3–4-month intervals, with transrectal ultrasound at 6-month intervals and repeat biopsy at 12–24 months. The active triggers for intervention include change in PSA kinetics, progression on follow-up biopsy, patient anxiety and clinical or radiographic evidence of local/distant progression.

In terms of upgrade-free survival, only about 20% of patients have a major change in CAPRA risk at the time of repeat biopsy. Treatment-free survival at 5 years is approximately 60% with overall survival of 98%, with 100% prostate cancer specific survival. Approximately 270 patients in the cohort underwent radical prostatectomy. A matched analysis shows that patients who progressed to 3+4 compared to those diagnosed with 3+4. In terms of PSA-free survival there is no difference among the cohort.

At UCSF it is thought that AS is appropriate for younger men. It turns out that younger patients have lower progression rates than older patients. Three-year and 5-year upgrade-free survival rates are 73% and 55%, respectively, versus 64% and 48% in the overall cohort. Young patients are more likely to receive subsequent treatment with RP (26%) versus radiotherapy (7%). There is no significant association between younger age and time to treatment or biochemical recurrence following delayed RP.

PSA is not a good predictor for upgrading. The PSA itself remains stable relatively early in surveillance. One of the strongest predictors of treatment is actually PSA density, which is a better predictor of treatment and reclassification than PSA.

With regard to serial imaging during AS, there are few reports of longitudinal radiographic progression during AS. In the experience of UCSF, 974 low and intermediate risk patients managed with AS receiving serial high resolution biplanar TRUS 228 eventually underwent RP. Progression by initial TRUS stage shows a change in the volume over time.

In tissue-based gene expression testing, UCSF has worked with various companies, including a quantitative 17-gene reverse transcription–polymerase chain reaction assay on manually micro-dissected tumor tissue from needle biopsy. Using the Oncotype DX Genomic Prostate Score (GPS) shows a wide distribution of GPS at each level of clinical risk. There is improved risk discrimination with addition of GPS to CAPRA. Serial oncotype testing on AS has been implemented and 98 men identified who underwent serial GPS testing. There was no difference with the GPS scores, even at the time of upgrade.

There is big interest in multiparametric magnetic resonance imaging (MRI) in the USA and the UK. MR targeted biopsy offers the potential to combine the anatomic and biological insights afforded by high resolution prostate MRI with real-time ultrasonographic guidance. There is enthusiasm for MR/ultrasound fusion-guided biopsy with ultrasound guided biopsy for the diagnosis of prostate cancer. Fusion biopsy helps to identify higher risk cancers.

In terms of anticipated opportunities and challenges for MRI fusion biopsy there are variable techniques and variable experience and there are also concerns about cost effectiveness. Comparing patients who had the fusion biopsy compared to the systematic biopsy, 12 patients (13%) were identified with upgraded cancers. Future avenues of investigation include the outcomes at subsequent biopsy following initial fusion MR biopsy, impact on risk stratification and cost considerations.

In terms of anxiety, depression and distress in RP versus AS, it has been shown that AS patients do not suffer abnormally from depression or anxiety. In terms of urinary function in low-risk disease, there is a change after RP, followed by gradual recovery, but not quite to pre-treatment function. In terms of sexual function it is important to note that sexual function declines with age, so RP and AS sexual function outcomes grow closer together as time progresses.

There is concern that focal therapy could lead to greater treatment being provided to low-risk patients. This is an issue that will require monitoring. In addition, online disease-management tools online are being developed for patients to report their outcomes and provide support. This is a trend that will require further attention.

7.1. Discussion

Declan Murphy asked about offering AS to younger men with intermediate risk. Peter Carroll noted that UCSF is careful to explain the risks and weigh up the alternatives. He noted that he was very concerned about relentless grade migration worldwide. In younger patients there are MRI testing and yearly fusion biopsies available, from which a low-risk cancer can be identified.

Osamu Ogawa asked about best follow-up protocol for AS. Peter Carroll responded that it is thought that AS can be made much more efficient and some patients may not need further biopsies, depending on their level of risk. The tendency is to see patients at 3-month intervals, but there is a feeling that this could be made more efficient and intervals further extended.

8. Closing remarks

Taiji Tsukamoto (Department of Urology, Sapporo Medical University) thanked all the participants for their input in the symposium and expressed his appreciation to Hideyuki Akaza for leading efforts to launch A-CaP.

Peter Carroll also thanked Hideyuki Akaza for organizing a wonderful symposium and expressed his expectations for a wonderful Asia-wide collaboration through A-CaP.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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